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04-10-01 #2

PATENT

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Catherine M. Peck March 12, 2001  
Catherine M. Peck Date

Applicants: Gassenmeier, et al.  
Serial No.: Not Yet Known 09800624  
Filed: March 7, 2001  
Examiner: Not Yet Known  
Art Unit: Not Yet Known  
Title: ORGANOLEPTIC COMPOUNDS: USE OF 3-MERCAPTO  
ALKANOIC ACID ESTERS AS FLAVOR INGREDIENTS  
Atty Docket: GRISA-710

Cincinnati, Ohio 45202

March 12, 2001

Assistant Commissioner for Patents  
Washington, D.C. 20231

SUBMISSION OF PRIORITY DOCUMENT

Sir:

Attached is a certified copy of Applicants' European Utility Patent No. 104904.8 filed on 8 March 2000, the right of priority of which has been and is claimed pursuant to the provisions of 35 U.S.C. § 119.

Applicants do not believe that any fees are due in connection with this response. However, if such petition is due or any fees are necessary, the Commissioner may consider this to be a request for such and charge any necessary fees to deposit account 23-3000.

Respectfully submitted,

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Bescheinigung

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Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

00104904.8

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
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**Blatt 2 der Bescheinigung**  
**Sheet 2 of the certificate**  
**Page 2 de l'attestation**

Anmeldung Nr.:  
Application no.: 00104904.8  
Demande n°:

Anmeldetag:  
Date of filing: 08/03/00 ✓  
Date de dépôt:

Anmelder:  
Applicant(s):  
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Bezeichnung der Erfindung:  
Title of the invention:  
Titre de l'invention:  
Organoleptic compositions

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:  
State:  
Pays:

Tag:  
Date:  
Date:

Aktenzeichen:  
File no.  
Numéro de dépôt:

Internationale Patentklassifikation:  
International Patent classification:  
Classification internationale des brevets:

/

Am Anmeldetag benannte Vertragsstaaten:  
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR  
Etats contractants désignés lors du dépôt:

Bemerkungen:  
Remarks:  
Remarques:

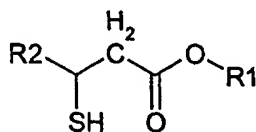
08 März 2000

Case 20598

### Organoleptic Compositions

The present invention relates to flavor or fragrance compositions comprising 3-mercapto carboxylic esters and/or precursors thereof and to a method of flavoring a food, a beverage or a consumer healthcare or household product using these compounds.

- 5 The Swiss patent 557 423 describes 3-mercapto carboxylic esters of the general formula I



wherein R1 represents an alkyl or alkenyl or alkadienyl group with 1 to 6 carbon atoms, and R2 represents an alkyl or alkenyl group containing 3 to 9 carbon atoms are known as flavor or fragrance compounds.

- 10 These compounds possess either green organoleptic properties, e.g. leaf green (3-mercapto-4-methylhexanoic acid ethyl ester), green fruity (3-mercapto-4-methylhexanoic acid hex-3-enyl ester), green and pungent (3-mercapto-4-methylhexanoic acid 2-hexenyl ester) or fatty organoleptic properties (e.g. 3-mercaptooctanoic acid ethyl ester, 3-mercaptononanoic acid methyl ester, 3-mercaptodecanoic acid ethyl ester or 3-mercapto-  
15 4-ethylhexanoic acid ethyl ester). But an exception represents 3-mercapto-4-methylhexanoic acid hexa-2,4-dienyl ester with a sulfurous, onion and garlic-like note. The latter mentioned compound demonstrates that a small change in the structure of the

compound can cause already a dramatically change of the odor properties, e.g. a hexa-2,4-dienyl group instead of a hex-3-enyl group changes the organoleptic character from green-fruity to onion, garlic-like.

The flavor and fragrance industry is still further interested in new ingredients with a clear  
5 fruity character. Thus, the above mentioned compounds would be of interest if they have not the disadvantage that the fruity note is always combined with green and/or fatty notes.

Surprisingly, it has now been found that compounds of formula I and precursors thereof, wherein R1 represents an alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R2 represents a methyl or an ethyl group, whereby the alkyl, alkenyl or alkadienyl  
10 group can be branched or unbranched, overcome the afore mentioned disadvantage and, hence, can be used as flavor or fragrance compounds with a clear fresh character. Thus, the present invention is directed to this subject matter. The compounds according to the invention can advantageously be used as ingredients for flavor or fragrance compositions as will be explained below. If the compounds contain double bonds, they can exist in any  
15 desired stereoconfiguration.

Preferred examples of R1 are methyl, ethyl, n- or iso-propyl, n- or iso- or tert-butyl, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl and n-octyl.

The compounds shall include the racemates as well as the pure enantiomers, which are defined by the asymmetric centre in beta position to the acid functionality.

20 Especially preferred compounds to be used as flavor or fragrance ingredients are 3-mercaptobutanoic acid methyl ester, 3-mercaptobutanoic acid ethyl ester, 3-mercaptobutanoic acid n-hexyl ester, (R)-3-mercaptobutanoic acid methyl ester, 3-mercaptobutanoic acid (Z)-3-hexenyl ester and 3-mercaptopentanoic acid ethyl ester, whereby 3-mercaptobutanoic acid methyl ester and 3-mercaptobutanoic acid ethyl ester  
25 are the most preferred ones.

Structurally, the compounds according to the invention differ from the compounds described in the afore mentioned Swiss patent in their chain length of the acid.

3-Mercaptoalkanoic acid esters according to the present invention are known in the literature, e.g. by the German Offenlegungsschrift 2 363 573. They are e.g. used as  
30 intermediates in the synthesis of pharmaceuticals (e.g. leukotrien antagonists and inhibitors of leukotrien biosynthesis as described by the European patent publication EP 0399818). Further, US patent 3,954,843 describes the general synthetic pathways for the production of the racemates and in Tetrahedron Letters, Vol 32, No.46, pp 6723-6726, 1991, the production of the pure enantiomere is described.

It has been found that the compounds of the present invention exhibit fruity properties, mainly in the range of passion fruit, cassis or tropical fruit which organoleptic properties have never been described before although the compounds themselves are already known as said already above. They differ strongly in their organoleptic properties from the  
5 compounds mentioned in Swiss patent 557 423 and in contrast to these the unwanted, disturbing green or fatty odor aspects are absent.

The preferred compounds according to the invention are the short chain compounds with a total maximum number of C-atoms of 7. They exhibit strong cassis-like and/or red fruit notes, which remind on passion fruit, black current and blackberry.

10 Compounds according to the invention with a total carbon atom number of equal to or greater than 8 are very substantive and, therefore, are specifically useful as ingredients in fragrances. They exhibit fresh-cassis and ripe-estery notes, and remind on grapefruit and/or citrus and/or Riesling wine.

It was found that the organoleptic properties of the R and S isomers are very similar.  
15 Therefore, from the economic point of view the easier and cheaper accessible racemates are preferred over the pure enantiomers.

Based on their clear fruity organoleptic properties the compounds are suitable for the creation of flavor and fragrance compositions. They can be combined in the usual manner with practically all available flavor or fragrance raw materials, i.e. synthetic and/or nature  
20 identical and/or natural substances and/or natural extracts and/or additional carrier materials and/or further additives used in the flavor or fragrance field.

Specifically, the very distinct berry and estery floral notes of the compounds according to the invention enable the production of specific and characteristic flavor profiles, which are new. These can be used for the aromatization of foodstuff, beverages, pharmaceuticals,  
25 oral hygiene products (e.g. toothpaste) or other healthcare products.

Further, specifically the compounds of the invention add a berry, fruity and some tropical aspects to fruit flavor compositions like peach, strawberry, passion fruit, citrus and raspberry. Thereby the body of the flavor is increased and its stability (longlastiness) improved. However, the use is not restricted to fruit flavors, but the compounds according  
30 to the invention can be combined also with herbal, mint and savoury flavors, whereby they increase especially the fullness, freshness and/or the herbal character. So, for example, in meat flavors they increase the natural meat aroma.

Due to their fruity odor characteristics the compounds of the invention can also be used in fragrance compositions like fine fragrances or perfumed products of all kinds, especially of

cosmetic articles, consumer healthcare or household products, as e.g. washing agents, detergents, soaps or toothpaste. Here, specifically the compounds according to the invention add an herbal-fruity and, surprisingly, also marine aspect to floral, musk and woody accords. At the same time the freshness is increased.

- 5 The preferred dosage range of the compounds according to the invention in a food, a beverage, a consumer healthcare or a household product is from 0.001 to 500 mg/kg, preferably 0.01 to 50 mg/kg. In fragrance compositions concentrations of the compound(s) according to the invention of from 0.001% to 30%, preferably from 0.01% to 10%, are preferably used.
- 10 Instead of directly using a compound of the invention as flavor or fragrance ingredient, it may be advantageous to use a precursor thereof, i.e. a chemical derivative of a compound according to the invention which can be easily transformed to the compound according to the invention. The precursors themselves can already be of sensorial interest. For example and preferably, as precursors the esters of 3-acylthio acids, which can be obtained by
- 15 treatment of the compounds according to the invention with acyl chloride, may be added to an aroma or food or fragrance composition. From the esters of 3-acylthioacids the compounds according to the invention can be released by enzymatic hydrolysis and/or chemical treatment. This reaction can take place either already in the flavor or fragrance composition or in the products containing these compositions.
- 20 The present invention is described further in the following examples which are presented solely for the non-limiting purpose of further illustrating the invention.

### Example 1

#### Synthesis of 3-mercaptopentanoic acid methyl ester

- 25 At 0°C, 5.71g of 2-pentenoic acid methyl ester were introduced in a 500mL round-bottom flask containing 200mL of dry methanol. A solution of 4.44g of NaSH·H<sub>2</sub>O and 2.57mL acetic acid in 100mL methanol was then added. The resulting orange mixture was stirred at room temperature for 2 days. Solution was then concentrated, taken in ether, washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated again and gave 7g of a
- 30 pale yellow oil containing about 38% of the desired compound which was purified by column chromatography.

### Example 2

Synthesis of (R)-3-mercaptoputanoic acid methyl ester.

The synthesis was done according to the description of Breitschuh, R.; Seebach, D. *Synthesis*, 1992, 83-89 as follows:

- 5 At 0°C, 82.31g of NaSH•H<sub>2</sub>O was added to a 1.5L round-bottom flask containing 600mL of distilled water. To this solution, 83.08g of (S)-β-butyrolactone were added over a period of 20 minutes. The mixture was stirred for 1h at 0°C and stayed overnight at room temperature. The solution was then brought to pH 2 and was extracted with ether. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give
- 10 110g of slightly yellow oil. In a 250mL flask, 30g of the oil previously obtained were dissolved in 80mL of methanol. A catalytic amount of sulfuric acid was added to the mixture, which was heated at reflux for 19h. The solution was then concentrated and partitioned between ether and cold brine. The organic layer was washed with sodium bicarbonate and brine, dried over MgSO<sub>4</sub>, filtered and concentrated and gave 35.2g of oil,
- 15 which was purified by chromatography on silica gel.

### Example 3

Synthesis of 3-acetylthiobutanoic acid hexyl ester

- At room temperature, in a 250-mL round-bottom flask with a gas outlet, 21 g of 3-
- 20 mercaptoputanoic acid hexyl ester were dissolved in 50mL of neat acetyl chloride. The mixture was stirred at room temperature for 6h. It was then cooled down to 0°C and the reaction was quenched by careful addition of 100 mL of dry methanol in small portions. The mixture was then washed with bicarbonate, dried over MgSO<sub>4</sub>, filtered and concentrated and gave the acetylated compound in 98% yield.

25

### Example 4

- To a tropical fruit soft drink of the following composition (a) containing the following fruit flavor (b) 0.1 mg/L 3-mercaptoputanoic acid methyl ester was added. Thereby, compared with the aroma note of the starting soft drink additionally a passion fruit
- 30 typical top note occurred and, at the same time, the freshness was increased significantly.



(a): Composition of typical tropical fruit soft drink:

	[g]
water:	9500
sugar syrup 65 Brix:	170
5 citric acid 50%:	5
sodium citrate:	0.4
sodium benzoate:	0.15
tropical fruit flavor (b):	0.3

10 (b): Composition of tropical fruit flavor

	[g]
benzaldehyde	4.0
linalool	4.0
(Z)-3-hexenyl butanoate	4.0
15 4-hydroxy-2,5-dimethyl- 2(5H)-dihydrofuran-3-one	8.0
ethyl butanoate	30.0
hexyl butanoate	24.0
ethyl hexanoate	14.0
20 1-phenylethyl acetate	9.8
3,7-dimethyl-2,6-octadienthiol	0.2
(Z)-3-hexenol	2.0
propylenglycol	900.0

### Example 5

For comparison to an orange soft drink (blank) of the composition as described below having an orange, aldehydic and soapy aroma on one hand 3-mercaptoputanoic acid methyl ester and on the other hand 3-mercaptoputanoic acid methyl ester, which is an  
5 example out of the group of compounds described by at the Swiss patent mentioned at the beginning and having a structure coming closest to the compound of the present invention, were added both at a level of 0.1 mg/L and both compared with the blank orange soft drink. The drink containing 3-mercaptoputanoic acid methyl ester exhibited an orange, mandarine, fresh squeezed juice note with strong fruity aspects, which is a  
10 significant improvement over the blank soft drink. In contrast thereto, the drink containing 3-mercaptoputanoic acid methyl ester exhibited a strong fatty sulfury-woody aroma with a grapefruit aspect.

#### Composition of orange soft drink:

15		[g]
	water:	9500
	sugar syrup 65 Brix:	170
	citric acid 50%:	5
	sodium citrate:	0.4
20	sodium benzoate:	0.15
	orange oil 40 fold:	0.005

### Example 6

To a woodberry flavored yoghurt (blank) consisting of components (a) and (b) as  
25 described below 3-mercaptoputanoic acid methyl ester and 3-mercaptoputanoic acid ethyl ester were added and compared with a yoghurt having an addition of 3-mercaptoputanoic acid methyl ester.

To the blank woodberry flavored yoghurt 0.2 mg/kg 3-mercaptoputanoic acid methyl ester was added. Compared with the blank woodberry favored yoghurt a strong red fruit note,

reminiscent on blackberry was present. An addition of 3-mercaptoputanoic acid ethyl ester at a level of 2 mg/kg to the blank woodberry flavored yoghurt increased the freshness and the overall flavor profile changed to blueberry. In contrast thereto an addition of 3-mercaptoputanoic acid methyl ester, i.e. a long chain 3-mercaptoputanoic acid ester as  
5 described by the prior mentioned Swiss patent, at a level of 0.2 mg/kg resulted in a soapy taste profile. At a level of 2 mg 3-mercaptoputanoic acid methyl ester per 1kg yoghurt yielded a fatty-meaty, sulfury aroma profile.

(a) Yoghurt (3.5 % fat, 10.0% sucrose) with 1g woodberry flavor per 1 kg yoghurt (b).

10	(b) Woodberry flavor	[ g]
	benzyl acetate	0.5
	ethyl acetate	4.0
	ethyl 3-metehylbutanoate	1.5
	(Z)-3-hexenol	0.1
15	alpha-ionone	0.2
	linalool	0.5
	3-methylbutyl 3-methylbutanoate	0.3
	4-(4-hydroxyphenyl)-2-butanone	2.0
	cylopentadecanolide	0.4
20	vanillin	0.5
	propylenglycol	90.0

#### Example 7

Comparison of two fragrance accords, either with 3-mercaptoputanoic acid methyl ester  
25 or with 3-mercaptoputanoic acid methyl ester.

To a clementine accord as described below 0.004 % (w/w) 3-mercaptoputanoic acid methyl ester was added. At that very low level the accord turned from orange-mandarine

to green clementine. The sample with addition of 3-mercaptoputanoic acid methyl ester was more sparkling, natural clementine and strongly increased the diffusivity. When the 3-mercaptoputanoic acid methyl ester was used instead, the diffusivity was much less, and a disturbing sulfury, fatty-meaty side note appeared.

5 Formula of clementine accord

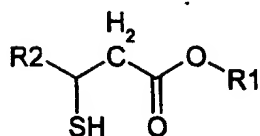
	rose oxide	1
	buchu leaf oil	2
	geranyl acetate	3
10	geranyl butyrate	3
	ethyl caprylate	4
	(E)-2-hexenale	4
	geranyl isobutyrate	4
	cinnamic aldehyd	5
15	oxane 5% in dipropylene glycol	5
	hexanale	6
	(Z)-3-hexenol	6
	linalool oxyd	6
	isoeugenol acetate	7
20	corps pampelmousse 10% in triethyl citrate	10
	benzaldehyde	15
	allyl hepatanoate	15
25	cinnamyl acetate	20
	beta ionone	24

	ethyl acetoacetate	60
	gamma undecalactone	80
	ethyl acetate	120
	labienoxime	200
5	lemon oil italy	600
	furonol 1% in triethyl citrate	1060
	orange oil 7-fold	2000
	orange oil brasil	2400
	dipropylene glycol	3340
10		-----
		10000

While the invention has been illustrated and described with respect to illustrative  
embodiments and modes of practice, it will be apparent to a person skilled in the art that  
15 various modifications and improvements may be made without departing from the scope  
and spirit of the invention. Accordingly, the invention is not to be limited by the  
illustrative embodiments and practice.

Claims

1. A flavor or fragrance composition comprising at least one compound of formula I



or a precursor thereof, wherein R1 represents a branched or unbranched alkyl, alkenyl or  
5 alkadienyl group containing 1 to 8 carbon atoms and R2 represents a methyl or an ethyl group.

2. The composition according to claim 1, wherein R1 is selected from the group consisting of methyl, ethyl, n- or iso-propyl, n- or iso- or tert-butyl, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl and n-octyl.

10 3. The composition according to claim 1, wherein at least one compound is selected from the group consisting of 3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid ethyl ester, 3-mercaptopentanoic acid n-hexyl ester, (R)-3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid (Z)-3-hexenyl ester and 3-mercaptopentanoic acid ethyl ester or a precursor thereof.

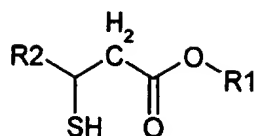
15 4. The composition according to claim 3, wherein at least one compound is 3-mercaptopentanoic acid methyl ester or 3-mercaptopentanoic acid ethyl ester.

5. The fragrance composition according to claim 1, wherein the total amount of carbon atoms of at least one compound of formula I is equal or greater 8.

20 6. The composition according to any one of the claims 1 to 4, wherein the precursor is performed by reaction of acyl chloride with the compound of formula I.

7. The fragrance composition of any one of the claims 1 to 6, wherein the concentration of the compound of formula I or of the precursor thereof is from 0.001% to 30%, preferably from 0.001% to 10%.

25 8. A method of flavoring a food, a beverage or a consumer healthcare or household product, wherein at least one compound of formula I



I

or a precursor thereof, wherein R1 represents a branched or unbranched alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R2 represents a methyl or an ethyl group, is added.

9. The method according to claim 8, wherein R1 is selected from the group consisting of methyl, ethyl, n- or iso-propyl, butyl n-, iso- or tert-, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl and n-octyl.

10. The method according to claim 9, wherein at least one compound is selected from the group consisting of 3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid ethyl ester, 3-mercaptopentanoic acid n-hexyl ester, (R)-3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid (Z)-3-hexenyl ester and 3-mercaptopentanoic acid ethyl ester or a precursor thereof.

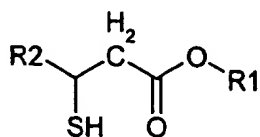
11. The method according to claim 9, wherein at least one compound is 3-mercaptopentanoic acid methyl ester or 3-mercaptopentanoic acid ethyl ester.

12. The method according to anyone of the claims 8 to 11, wherein the precursor is performed by reaction of acyl chloride with the compound of formula I.

13. The method of any one of the claims 8 to 12, wherein the compound(s) of formula I or the precursor(s) thereof is/are present in an amount of 0.001 mg/kg to 500 mg/kg food, beverage or consumer healthcare or household product, preferably in an amount of 0.01 mg/kg to 50 mg/kg food, beverage or consumer healthcare or household product.

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The present invention relates to flavor or fragrance composition comprising at least one compound of the formula I



I

- 5 or a precursor thereof, wherein R1 represents a branched or unbranched alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R2 represents a methyl or an ethyl group and to a method of flavoring a food, a beverage or a consumer healthcare or household product using at least one of these compounds.